Comprehensive genomic profiling of mucinous ovarian carcinoma with comparisons to mucinous colorectal carcinoma

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Abstract

Background

Advanced mucinous ovarian cancer (mOC) is a chemoresistant disease with poor outcomes compared to serous ovarian cancer (sOC). It is often confused with mucinous colorectal carcinoma (mCRC) metastatic to the ovary. Studies have explored CRC chemo regimens for the treatment of mOCs due to their histologic similarities. Herein we use comprehensive technologies to further our understanding of mOC.

Methods

140 mOC specimens were evaluated by Caris Life Sciences from 2015 - 2018 using next generation sequencing (NGS), fragment analysis (FA), in situ hybridization (ISH), and immunohistochemistry (IHC). 188 mCRC were used for comparison. Chi square analysis was conducted using SPSS.

Results

The most frequent mutations in mOC were KRAS (64.7%), TP53 (56.0%), ARID1A (50.0%), CDKN2A (18.7%), PIK3CA (11.7%), and ATM (8.2%). ERBB2 (HER2) amplification was 12.2%, BRCA1 and BRCA2 mutation rates were 0.0 and 2.4%. Markers of immunogenicity were rare: MSI-H in 4.2%, high tumor mutational burden (TMB) in 4.8%, and PD-1 expression in 5.3%.

Significant differences between mOC and CRC were found in the following pathways: Wnt (APC: 4.7 vs 61.7%), PI3K/AKT/mTOR (ARID1A: 50.0 vs 0.0% and FBXW7: 3.7 vs 12.5%), MAPK (JRAF: 2.4 vs 11.9%), cell cycle control (CDKN2A: 18.7 vs 0.0%), as well as in ERBB2 (HER2) amplification (12.2 vs 0.0%), and hormone receptor expression (ER: 12.8 vs 0.0%, PR: 15.9 vs 0.0%). High rates of KRAS (64.7, 73.5%) and TP53 (56.0, 46.7%) mutations were common to both tumor types.

Compared to mOC, right-sided CRC were more likely to have mutations in CDH1 (0.0 vs 6.7%) and PTPCH1 (0.0 vs 6.7%), while left-sided CRC were more likely to have mutations in FOXO3 (0.0 vs 5.9%) and IDH2 (0.0 vs 5.9%).

Conclusions

- Our findings suggest that mOC is genomically distinct from mCRC and has multiple potential targets.
- At the molecular level, mOC may be differentiated from mCRC in cases of uncertain primary tumor
- A phenotype analysis with the presence of ARID1A, CDKN2A, HER2, ER or PR distinguishes mOC from mCRC, as does the absence of CDH1, FOXO3, or IDH2.
- Dysregulation of the PI3K/AKT/mTOR, cell cycle control, MAPK, and hormonal pathways may represent actionable targets in mOC.
- Understanding the molecular profile of this relatively uncommon histology may help direct future therapeutic trials in mOC.

References


Authorship

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